Study Title: Stimulation of the prefrontal cortex reduces intentions to commit aggression: A randomized, double-blind, placebo-controlled, stratified, parallel-group trial

NCT02427672

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Materials and Methods

Trial Design

The study consisted of a double-blind, placebo-controlled, stratified, randomized trial comparing an anodal tDCS intervention with a sham control group. Baseline assessments and one session of tDCS or sham intervention were conducted during the experimental session, while outcome measures were assessed the following day. Tasks and questionnaires were administered in a fixed order. The study was approved by the Institutional Review Board of the University of Pennsylvania and the trial protocol was registered at ClinicalTrials.gov (NCT02427672).

Participants

Eighty-six healthy adults (≥ 18 years of age) were recruited in Philadelphia between April 2015 and April 2016. The experiment took place during the course of one visit to the study site. In addition to assessments conducted at baseline, participants were followed up one day after the experimental session using a web-based questionnaire. Exclusion criteria included contraindications to brain stimulation, including metallic implants near the electrode sites, unstable medical conditions, neurological, cardiovascular, or psychiatric illness, participation in another non-invasive brain stimulation study on the same day, history of adverse reactions to tDCS, and lack of email access. Written informed consent was obtained from all participants.

tDCS Intervention

tDCS was administered by trained study personnel using a battery-driven, constant-current stimulator (TCT Research). Two anodal electrodes were placed over the DLPFC bilaterally (F3 and F4) according to the International 10-20 EEG system. A constant current of 2mA (1mA to each DLPFC site) was applied for 20 minutes through saline-soaked sponge electrodes (5x5cm). A single extracephalic cathodal electrode (5x7cm) was placed at the posterior base of the neck in order to minimize unintentional effects of inhibitory stimulation on brain activity.

Following standard tDCS protocol, stimulation commenced after a 30-second ramp-up period. The current was ramped down over the last 2 seconds. The tasks performed during tDCS are understood to influence the behavioral after-effects of stimulation (Gill et al., 2015). Thus, during the stimulation session, all participants performed the Psychology Experiment Building Language (Mueller and Piper, 2014) version of two cognitive tasks that are known to engage the DLPFC, the Psychomotor Vigilance Task (Dinges and Powell, 1985; Cui et al., 2015), followed by the Iowa Gambling Task (Bechara et al., 1994; Ernst et al., 2002). Although participants in both intervention arms received the same electrode placement and ramp-up/down times, stimulation for the sham control group was discontinued after 30 seconds. This has proven to be effective for blinding as participants habituate to the sensation of stimulation within seconds of current initiation (Gandiga et al., 2006).

Intentions to commit aggression. Behavioral intentions to commit aggressive acts were assessed using two hypothetical vignettes, which have been studied in samples with similar

characteristics to ours (Hannon et al., 2000; Mazerolle et al., 2003). Brief scenarios describing two types of aggression, physical assault and sexual assault, were presented to participants who responded to the anticipated likelihood that they would commit the aggressive act. Responses were measured on a scale ranging from zero (no chance at all) to ten (100 percent chance).

Perceptions of moral wrongfulness. To assess moral perceptions of the aggressive acts, participants were asked to rate how morally wrong it would be to act as the protagonist in the scenario on a scale from 0 (not at all) to 10 (very). Aggregate measures of aggressive intent and perception of moral wrongfulness were created by combining responses from the physical and sexual assault scenarios (Armstrong and Boutwell, 2012).

Aggression. The voodoo doll task is a reliable and validated behavioral analog measure of aggression (DeWall et al., 2013). In this task, participants were shown a computer-based image of a doll that represented a partner or a close friend. They were told that they were given the opportunity to release their negative energy to that individual by inserting as many pins (0-51) in the doll as they wished. Instructions did not use the word "voodoo". Stabbing the doll with more pins indicated higher levels of aggression.

Randomization and Stratification

At the initial visit, participants were randomized into an active stimulation or sham/placebo condition using a computerized urn randomization procedure (Stout et al., 1994). The stratification factors were age (18 years/19 years/20 years and above), sex (male/female),

and ethnicity (Caucasian/non-Caucasian). This stratification was used to balance groups on key demographic variables.

Blinding

Participants and experimenters were blind to the tDCS condition assignment. The trial adhered to established procedures to maintain separation between staff that conducted the stimulation and staff that engaged with the participant. In each experimental session, only one experimenter who set up the tDCS procedure had knowledge of the participant's allocation. To further ensure blinding, all participants were kept blind to the objective of the study and outcome measures were not taken in the presence of research staff as they could lead to biased results.

In the 3 cases where double blinding was compromised due to the inability of having more than one experimenter at a session, the cases were excluded from analyses. To assess adherence to blinding procedures, James' (James et al., 1996) and Bangs' (Bang et al., 2004) blinding indices were calculated using the participants' and blinded experimenters' guesses about group assignment at the end of the experimental session.

Statistical Analysis Plan

One-way ANCOVA was used to test group differences in intentions to commit aggression and the behavioral measure of aggression. Baseline measures were examined as possible covariates: variety of crime throughout the lifetime, aggression, GPA, trait anxiety, social adversity, psychopathy, the lack of premeditation and sensation-seeking dimensions of impulsivity, and self-control.

In addition to a Self-Report Crime Questionnaire that asked participants to indicate the number of times they had committed 36 criminal and delinquent acts ranging from white-collar and blue-collar offenses (e.g. fraud and shoplifting) to non-criminal, deceptive behaviors (e.g., cheating on an exam), participants' baseline levels of aggression were assessed using the Reactive-Proactive Aggression Questionnaire (Raine et al., 2006). Trait anxiety was assessed using the 20-item Spielberger State-Trait Anxiety Inventory (Spielberger, 1983). A social adversity index was obtained based on responses to 14 items obtained from demographic questionnaires. Items included parent unemployment, mother's low education, father's low education, parental separation or divorce, placement in a foster home, hospital, or other institution during childhood, having 5 or more siblings, born to a teenage mother, a ratio of people per room (including bedrooms, living room, dining room, and kitchen) of 1.0 and above, brought up in public housing, parents' use of welfare or food stamps from the government, father or mother had been arrested, father or mother has had problems with alcohol or drugs, father or mother has had physical illness, such as heart or lung problems, father or mother has had mental illness, such as alcoholism, major depression, schizophrenia, or anxiety. To assess psychopathic traits, the short form of the Self-Report of Psychopathy-III (SRP-SF) questionnaire, comprising 29 items, was administered (Paulhus et al., 2009). Additionally, scores were obtained from the lack of premeditation and sensation-seeking subscales of the short-form version of the UPPS-P Impulsivity Scale (SUPPS-P) (Lynam, 2013), and self-control was assessed using the 13-item Brief Self-Control Scale (Tangney et al., 2004).

Following recommendations, stratification variables and baseline measures that were associated with the outcomes were adjusted for, while variables with baseline imbalances were

not (Committee for Proprietary Medicinal Products, 2004; Kahan et al., 2014). Effect sizes were calculated using partial eta squared.

To provide information on a mechanism of action accounting for any effect of tDCS on aggressive intent, change in perceptions of moral wrongfulness was examined using ANCOVA. We tested whether enhanced moral judgment mediated group differences in intent to commit aggressive acts through a bootstrapping approach using the PROCESS macro on SPSS (Hayes, 2013). 10,000 bootstrapped samples were drawn from the original data. The indirect effect of tDCS on intent to commit aggression was calculated as the product of the regression coefficients for the relationship between tDCS and moral judgment and the association between moral judgment and aggressive intent. The percent mediated, P_M, is expressed as the ratio of the indirect to total effect of treatment group on intention to commit aggression (Ditlevsen et al., 2005; Hayes, 2013). Hypothesis tests were two-tailed. Blinding indices were obtained using STATA version 14.0 (Stata Corp, 2015). All other statistical analyses were conducted using SPSS version 24.0 (IBM Corp, 2016).